IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Applicant(s): Robert MARTUZA *et al.*

Title: **REPLICATION-COMPETENT HERPES SIMPLEX VIRUS MEDIATES DESTRUCTION OF NEOPLASTIC CELLS**

Appl. No.: 10/788,410

Filing Date: 3/1/2004

Examiner: SHEN, Wu Cheng Winston

Art Unit: 1632

Conf. No.: 4953

REPLY BRIEF

MAIL STOP APPEAL BRIEF - PATENTS
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Sir:

Under the provisions of 37 C.F.R. § 41.39, this Reply Brief is submitted in response to the Examiner's Answer dated April 13, 2011. Although Appellants believe that no fee is required, authorization is hereby given to charge any deficiency (or to credit any balance) to the undersigned deposit account 19-0741.

RELATED APPEALS AND INTERFERENCES

No related interferences are pending. The appeal in a commonly owned application, serial No. 11/097,391, is no longer pending, and prosecution of that application has been reopened.

STATUS OF CLAIMS

Claims 1-15, 17, and 21-27 are canceled. Claims 16, 18-20, and 28-32 are pending. Claims 16, 18-20, and 28-32 are at least twice rejected and are the subject of this appeal.

GROUNDS OF REJECTION TO BE REVIEWED ON APPEAL

The rejections to be reviewed on appeal are:

(i) the rejection of claims 16, 28 and 29 under 35 U.S.C. 103(a) over U.S. Patent No. 6,172,047 to Roizman *et al.* ("Roizman") in view of Vile *et al., Ann. Oncol.* 5 Suppl. 4: 59-65 (1994) ("Vile");

(ii) the rejection of claims 18-20 under 35 U.S.C. 103(a) over Roizman in view of Vile, and further in view of Chang *et al., Virology* 185(1): 437-440 (1991) ("Chang"); and

(iii) the rejection of claims 30-32 under 35 U.S.C. 103(a) over Roizman in view of Vile, and further in view of WO 92/14821 by McKay *et al.* ("McKay") and U.S. Patent No. 5,639,656 to Wright, Jr. ("Wright").

ARGUMENT

Pursuant to 37 C.F.R. §41.39, Appellants respond to aspects of the Examiner's Answer dated April 13, 2011 ("the Answer"). All arguments submitted in the Appeal Brief but not repeated here are incorporated by reference.

Appellants and the Examiner differ primarily on whether, in view of the *a priori* unpredictable aspect of the claimed invention, it still would have been obvious for the skilled artisan to combine the teachings of the cited references, thereby arriving at the claimed invention. Based on the considerations advanced in the Appeal Brief and elaborated upon here, Appellants renew their request that the Board resolve in Appellant's favor the ultimate legal question of obviousness under 35 U.S.C. §103(a) .

Much of the Answer is taken up with the Examiner's repeating what he views as the essence of the rejection rationale, which Appellants addressed in the Appeal Brief. As Appellants demonstrated previously, the Examiner's assertions on various technical issues generally lack valid factual support.

Beyond those unsupported contentions, the main disputed issue for Appellants has remained the Examiner's consistent failure to take into account, on one hand, the nascent state of relevant art and, on the other hand, the unexpected or unpredictable aspect of the claimed invention. In light of that art the skilled artisan would have had no reason to combine (indeed, was disincentivized from combining) oncolytic therapy and cytokine expression, both of which are design parameters or considerations that the claimed invention embodies. "Disincentivized" is an apt characterization (i) because oncolytic therapy would lyse host cells, yet cytokine expression would require intact host cells to express the cytokine-encoding gene (see Appeal Brief, at page 9, 2nd full paragraph), and (ii) because the presence of a cytokine was expected to protect host cells from HSV infection and replication, thereby counteracting desired oncolytic effects (*id.*, last full paragraph).

The Examiner has never come to grips with the significance of these conflicting considerations (i) and (ii) in the context of oncolytic virotherapeutics, the new, relatively undeveloped field to which the claimed invention most closely relates. Instead, the Examiner for the first time relies on JP 8-127542, in an attempt to counter Appellants' point about the conventional wisdom's recommending against the recited combination of cytokine-expression capability in an oncolytic HSV vector. See the Answer at page 18.

According to the Examiner, "oncolytic viral therapy and cytokine gene therapy are two closely related research fields as exemplified by JP 8-127542 . . . rather than two unrelated fields as Appellant argues." *Id.*, lines 18-20. It have never been Appellant's position that these "fields" were "unrelated," however, but instead that the prior art would have led the skilled artisan away from combining what were deemed disparate design elements drawn from each field.

The Examiner's belated invocation JP 8-127542 also is of no moment on the merits, since the Japanese reference is similar to the previously cited secondary reference, Vile, in having nothing to do with oncolytic therapy. As the Appeal Brief stated, Vile discloses not an oncolytic viral therapy but rather an *in situ* gene therapy, employing a tissue-specific promoter. See Vile's abstract as well as the Appeal Brief at page 11, last full paragraph.

The newly cited Japanese publication likewise is silent as to cytokine expression in the context of an ***oncolytic virus***. Instead, JP 8-127542 relates the expression of a cytokine in a ***viral delivery vector***, such as adenovirus or retrovirus. See JP 8-127542 at paragraph [0004] on page 2, at paragraph [0009] bridging pages 3 and 4, and at paragraph [0010] on page 4. At the time of filing the present application, there was no evidence that would have recommended either adenovirus or retrovirus to the skilled artisan as a candidate oncolytic virus. Unlike an oncolytic virus such as HSV, adenovirus and retrovirus do not lyse host cells.

Not surprisingly, the Examiner cited no publication, before the present application, that demonstrates any property qualifying adenovirus or retrovirus as an oncolytic virus. Thus, the skilled artisan would not have inferred from the teachings of JP 8-127542 that an oncolytic virus

could have been used as a delivery vehicle to replace the disclosed adenovirus or retrovirus. Again, the Examiner lacks factual support in his reading of JP 8-127542 to suggest anything of contemporaneous relevance to oncolytic viral therapy, *circa* June of 1994.

CONCLUSION

Absent impermissible hindsight, the skilled artisan would not have been motivated to combine seemingly disparate therapeutic elements in the manner of the claimed invention. Accordingly, Appellants renew their request for the Board to reverse the rejection in whole, passing the appealed claims on to issuance.

Respectfully submitted,

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